Hopf bifurcation analysis for a mathematical model of P53-MDM2 interaction

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Abstract

In this paper we analyze a simple mathematical model which describes the interaction between the proteins p53 and Mdm2. For the stationary state we discuss the local stability and the existence of the Hopf bifurcation. Choosing the delay as a bifurcation parameter we study the direction and stability of the bifurcating periodic solutions. Some numerical examples and the conclusions are finally made.

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1. Introduction

In every normal cell, there is a protective mechanism against tumoral degeneration. This mechanism is based on the P53 network. P53, also known as "the guardian of the genome", is a gene that codes a protein in order to regulate the cell cycle. The name is due to its molecular mass: it is a 53 kilo Dalton fraction of cell proteins. Mdm2 gene plays a very important role in P53 network. It regulates the levels of intracellular P53 protein concentration through a feedback loop. Under normal conditions the P53 levels are kept very low. When there is DNA damage the levels of P53 protein rise and if there is a prolonged elevation the cell shifts to apoptosis, and if there is only a short elevation the cell cycle is arrested and the repair process is begun. The first pathway protects the cell from tumoral transformation when there is a massive DNA damage that cannot be repaired, and the second pathway protects a number of important cells (neurons, myocardic cells) from death after DNA damage. In these cells first pathway, apoptosis, is not an option because they do not divide in adult life and their importance is obvious. Due to its major implication in cancer prevention and due to the actions described above, P53 has been intensively studied in the last two decades.

During the years, several models which describe the interaction between P53 and Mdm2 have been studied. We mention some of them in references [2], [3], [4], [6], [7], [8], [9], [10]. This paper gives a mathematical approach to the model described in [10]. The authors of paper [10] make a molecular energy calculation based on the classical force fields, and they also use chemical reactions constants from literature. Their results obtained by simulations in accordance with experimental behavior of the P53-Mdm2 complex, but they lack the mathematical part which we develop in this paper. We analyze the Hopf bifurcation with time delay as a bifurcation parameter using the methods from [1], [5], [7].

The paper is organized as follows. We present the mathematical model in section 2 and the existence of the stationary state is study. In section 3, we discuss the local stability for the stationary state of system (2) and we investigate the existence of the Hopf bifurcation for system (2) using time delay as the bifurcation parameter. In section 4, the direction of Hopf bifurcation is analyzed according to the normal form theory and the center manifold theorem introduced by Hassard [5]. Numerical simulations for confirming the theoretical results are illustrated in section 5. Finally, some conclusions

are made.

2. The mathematical model and the stationary state

The state variables are: $y_1(t), y_2(t)$ the total number of p53 molecules and the total number of Mdm2 proteins.

The interaction function between P53 and MDM2 is $f : \mathbb{R}_+^2 \to \mathbb{R}$ given by [10]:

$$f(y_1, y_2) = \frac{1}{2}(y_1 + y_2 + k - \sqrt{(y_1 + y_2 + k)^2 - 4y_1y_2}). \tag{1}$$

The parameters of the model are: s the production rate of p53, a the degradation rate of p53 (through ubiquitin pathway), and also the rate at which Mdm2 re-enters the loop, b the spontaneous decay rate of p53, d the decay rate of the protein rate Mdm2, k_1 the dissociation constant of the complex P53-Mdm2, c the constant of proportionality of the production rate of Mdm2 gene with the probability that the complex P53-Mdm2 is build. These parameters are positive numbers.

The mathematical model is described by the following differential system with time delay [10]:

$$\begin{aligned} \dot{y}_1(t) &= s - af(y_1(t), y_2(t)) - by_1(t), \\ \dot{y}_2(t) &= cg(y_1(t-\tau), y_2(t-\tau)) - dy_2(t), \end{aligned} \tag{2}$$

where f is given by (1) and $g : \mathbb{R}_+^2 \to \mathbb{R}$, is

$$g(y_1, y_2) = \frac{y_1 - f(y_1, y_2)}{k_1 + y_1 - f(y_1, y_2)}. \tag{3}$$

For the study of the model (1) we consider the following initial values:

$$y_1(\theta) = \varphi_1(\theta), y_2(\theta) = \varphi_2(\theta), \theta \in [-\tau, 0],$$

with $\varphi_1, \varphi_2 : [-\tau, 0] \to \mathbb{R}_+$ are differentiable functions.

In the second equation of (2) there is delay, because the trancription and translation of Mdm2 last for some time after that p53 was bound to the gene.

The stationary state $(y_{10}, y_{20}) \in \mathbb{R}_+^2$ is given by the solution of the system of equations:

$$
\begin{aligned}
&s - af(y_1, y_2) - by_1 = 0, \\
&cg(y_1, y_2) - dy_2 = 0.
\end{aligned} \tag{4}
$$

From (1), (3) and (4) we deduce that the stationary state can be found through the intersection of the curves:

$$
y_2 = f_1(y_1), \quad y_1 = f_2(y_1), \tag{5}
$$

where $f_1, f_2 : \mathbb{R}_+ \to \mathbb{R}$ are given by:

$$
\begin{aligned}
f_1(y_1) &= \frac{c(y_1(a+b) - s)}{d(k_1 a + (a+b)y_1 - s)}, \\
f_2(y_2) &= \frac{(s - by_1)(ka + (a+b)y_1 - s)}{a((a+b)y_1 - s)}.
\end{aligned} \tag{6}
$$

Proposition 1. *The function f_1, f_2 from (6) have the following properties:*

(i) f_1 is strictly increasing, f_2 is strictly decreasing on $\left(\frac{s}{a+b}, \frac{s}{b}\right)$;

(ii) There is a unique value $y_{10} \in \left(\frac{s}{a+b}, \frac{s}{b}\right)$ so that $f_1(y_{10}) = f_2(y_{10})$, where y_{10} is the solution of the equation $\varphi(x) = 0$, from $\left(\frac{s}{a+b}, \frac{s}{b}\right)$ where

$$
\varphi(x) = ac((a+b)x - s)^2 - d(k_1 a + (a+b)x - s)(ka + (a+b)x - s)(s - bx). \tag{7}
$$

Proof. (i) From (6) we have:

$$
\begin{aligned}
f_1'(y_1) &= \frac{(a+b)ack_1}{d(k_1 a + (a+b)y_1 - s)^2}, \\
f_2'(y_2) &= -\frac{b}{a} - \frac{bk}{(a+b)y_1 - s} - \frac{k(a+b)(s - by_1)}{((a+b)y_1 - s)^2}.
\end{aligned} \tag{8}
$$

For $y_1 \in \left(\frac{s}{a+b}, \frac{s}{b}\right)$, the relations (8) lead to $f_1'(y_1) > 0$, $f_2'(y_1) < 0$, so that f_1 is strictly increasing and f_2 is strictly deceasing.

(ii) By (i) there is $y_{10} \in \left(\frac{s}{a+b}, \frac{s}{b}\right)$ so that $f_1(y_{10}) = f_2(y_{10})$. From (6) and (7) it results that:

$$
\varphi(y_1) = f_{12}(y_1)h(y_1),
$$

where

$$h(y_1) = ad((a+b)y_1 - s)((a+b)y_1 + k_1 a - s)$$
$$f_{12}(y_1) = f_1(y_1) - f_2(y_1).$$

On $\left(\frac{s}{a+b}, \frac{s}{b}\right)$, the functions f_{12} and h are strictly increasing and consequently φ is strictly increasing. Because $\varphi(\frac{s}{a+b}) = -\frac{a^3 dkk_1 s}{a+b} < 0$ and $\varphi(\frac{s}{b}) = \frac{a^3 cs^2}{b^2} > 0$ we can conclude that equation $\varphi(x) = 0$ has a unique solution y_{10} on $\left(\frac{s}{a+b}, \frac{s}{b}\right)$.

3. The analysis of the stationary state and the existence of the Hopf bifurcation.

We consider the following translation:

$$y_1 = x_1 + y_{10}, y_2 = x_2 + y_{20}$$

and system (2) can be expressed as:

$$\begin{aligned} \dot{x}_1(t) &= s - af(x_1(t) + y_{10}, x_2(t) + y_{20}) - b(y_1(t) + y_{10}), \\ \dot{x}_2(t) &= cg(x_1(t-\tau) + y_{10}, x_2(t-\tau) + y_{20}) - d(x_2(t) + y_{20}). \end{aligned} \tag{9}$$

System (9) has a unique stationary state $(0,0)$. To investigate the local stability of the equilibrium state we linearize system (9). Let $u_1(t)$ and $u_2(t)$ be the linearized system variables. Then (9) is rewritten as:

$$\dot{U}(t) = AU(t) + BU(t-\tau), \tag{10}$$

where

$$A = \begin{pmatrix} -(b + a\rho_{10}) & -a\rho_{01} \\ 0 & -d \end{pmatrix}, B = \begin{pmatrix} 0 & 0 \\ c\gamma_{10} & c\gamma_{01} \end{pmatrix} \tag{11}$$

with $U(t) = (u_1(t), u_2(t))^T$ and ρ_{10}, ρ_{01}, γ_{10}, γ_{01} are the values of the first order derivatives for the functions:

$$f(x,y) = \frac{1}{2}(x + y + k - \sqrt{(x+y+k)^2 - 4xy})$$

and

$$g(x,y)=\frac{x-f(x,y)}{k_1+x-f(x,y)}$$

evaluated at (y_{10},y_{20}).

The characteristic equation corresponding to system (10) is $\Delta(\lambda,\tau)=det(\lambda I-A-e^{-\lambda\tau}B)=0$ which leads to:

$$\lambda^2+p_1\lambda+p_0-(q_1\lambda+q_0)e^{-\lambda\tau}=0, \tag{12}$$

where

$$\begin{array}{l} p_1=b+d+a\rho_{10}, \quad p_0=d(b+a\rho_{10}), \quad q_1=c\gamma_{01}, \\ q_0=c\gamma_{01}(b+a\rho_{10})-ac\rho_{01}\gamma_{10}. \end{array}$$

If there is no delay, the characteristic equation (12) becomes:

$$\Delta(\lambda,0)=\lambda^2+(p_1-q_1)\lambda+p_0-q_0. \tag{13}$$

Then, the stationary state $(0,0)$ is locally asymptotically stable if

$$p_1-q_1>0, \quad p_0-q_0>0. \tag{14}$$

When $\tau>0$, the stationary state is asymptotically stable if and only if all roots of equation (12) have a negative real part. We are determining the interval $[0,\tau_0)$ so that the stationary state remain asymptotically stable.

In what follows we study the existence of the Hopf bifurcation for equation (10) choosing τ as the bifurcation parameter. We are looking for the values τ_0 of τ so that the stationary state $(0,0)$ changes from local asymptotic stability to instability or vice versa. We need the pure imaginary solutions of equation (12). Let $\lambda=\pm i\omega_0$ be these solutions and without loss of generality we assume $\omega_0>0$. Replacing $\lambda=i\omega_0$ and $\tau=\tau_0$ in (12) we obtain:

$$\begin{array}{l} q_0cos\omega_0\tau_0+q_1\omega_0sin\omega_0\tau_0=p_0-\omega_0^2 \\ q_0sin\omega_0\tau_0-q_1\omega_0cos\omega_0\tau_0=-\omega_0p_1, \end{array}$$

which implies that

$$\tau_0=\frac{1}{\omega_0}\left((2k+1)\pi+arcsin\frac{p_1\omega_0}{\sqrt{(p_0-\omega_0^2)^2+\omega_0^2p_1^2}}+arcsin\frac{q_1\omega_0}{\sqrt{(p_0-\omega_0^2)^2+\omega_0^2p_1^2}}\right) \tag{15}$$

where ω_0 is a solution of the equation:

$$\omega^4 + (-p_1^2 - 2p_0 + q_1^2)\omega^2 + p_0^2 - q_0^2 = 0.$$

Now we have to calculate $Re\left(\frac{d\lambda}{d\tau}\right)$ evaluated at $\lambda = i\omega_0$ and $\tau = \tau_0$. We have:

$$\frac{d\lambda}{d\tau}|_{\lambda=i\omega_0,\tau=\tau_0} = M + iN$$

where

$$M = \frac{q_1^2\omega_0^6 + 2q_0^2\omega_0^4 + (p_1^2q_0^2 - p_0^2q_1^2 - 2p_0q_0^2)\omega_0^2}{l_1^2 + l_2^2} \tag{16}$$

and

$$\begin{aligned} N \;=\; & \frac{-q_1^2\tau_0\omega_0^7 + \omega_0^5(q_0q_1 - p_1q_1^2 + \tau_0(2p_0q_1^2 - p_1^2q_1^2 - q_0^2))}{l_1^2 + l_2^2} + \\ + \; & \frac{\omega_0^3(-p_1q_0^2 - 2p_0q_0q_1 + p_1^2q_0q_1 - p_0p_1q_1^2 + \tau_0(-p_1^2q_0^2 - q_1^2p_0^2 + 2p_0q_0^2))}{l_1^2 + l_2^2} + \\ + \; & \frac{\omega_0(-p_0p_1q_0^2 + p_0^2q_0q_1 - \tau_0p_0^2q_0^2)}{l_1^2 + l_2^2} \end{aligned} \tag{17}$$

with

$$l_1 = -q_1\omega_0^2 + p_1q_0 - q_1p_0 + \tau_0(-q_1p_1\omega_0^2 - q_0\omega_0^2 + q_0p_0),$$
$$l_2 = 2\omega_0q_0 + \tau_0(-q_1\omega_0^3 + p_0q_1\omega_0 + p_1q_0\omega_0).$$

We conclude with:

Theorem 1. *If there is no delay, under condition (14) system (10) has an asymtotically stable stationary state. If $\tau > 0$ and $p_1^2q_0^2 - q_1^2p_0^2 - 2p_0q_0^2 > 0$ then there is $\tau = \tau_0$ given by (15) so that $Re\left(\frac{d\lambda}{d\tau}\right)_{\lambda=i\omega_0,\tau=\tau_0} > 0$ and therefor a Hopf bifurcation occurs at (y_{10}, y_{20}).*

4. Direction and stability of the Hopf bifurcation

In this section we describe the direction, stability and the period of the bifurcating periodic solutions of system (2). The method we use is based on the normal form theory and the center manifold theorem introduced by Hassard [5]. Taking into account the previous section, if $\tau = \tau_0$ then all roots

of equation (11) other than $\pm i\omega_0$ have negative real parts, and any root of equation (11) of the form $\lambda(\tau) = \alpha(\tau) \pm i\omega(\tau)$ satisfies $\alpha(\tau_0) = 0$, $\omega(\tau_0) = \omega_0$ and $\dfrac{d\alpha(\tau_0)}{d\tau} \neq 0$. For notational convenience let $\tau = \tau_0 + \mu, \mu \in \mathbb{R}$. Then $\mu = 0$ is the Hopf bifurcation value for equations (2).

The Taylor expansion at (y_{10}, y_{20}) of the right members from (9) until the third order leads to:

$$\dot{x}(t) = Ax(t) + Bx(t-\tau) + F(x(t), x(t-\tau)), \tag{18}$$

where $x(t) = (x_1(t), x_2(t))^T$, A, B are given by (11) and

$$F(x(t), x(t-\tau)) = (F^1(x(t)), F^2(x(t-\tau)))^T, \tag{19}$$

where

$$\begin{aligned} F^1(x_1(t), x_2(t)) &= -\frac{a}{2}[\rho_{20}x_1^2(t) + 2\rho_{11}x_1(t)x_2(t) + \rho_{02}x_2^2(t)] - \\ &- \frac{a}{6}[\rho_{30}x_1^3(t) + 3\rho_{21}x_1^2(t)x_2(t) + 3\rho_{12}x_1(t)x_2^2(t) + \rho_{03}x_2^3(t)] \end{aligned}$$

$$\begin{aligned} F^2(x_1(t-\tau), x_2(t-\tau)) &= \frac{c}{2}[\gamma_{20}x_1^2(t-\tau) + 2\gamma_{11}x_1(t-\tau)x_2(t-\tau) + \\ &+ \gamma_{02}x_2^2(t-\tau)] + \\ &+ \frac{c}{6}[\gamma_{30}x_1^3(t-\tau) + 3\gamma_{21}x_1^2(t-\tau)x_2(t-\tau) + \\ &+ 3\gamma_{12}x_1(t-\tau)x_2^2(t-\tau) + \gamma_{03}x_2^3(t-\tau)] \end{aligned}$$

and ρ_{ij}, γ_{ij}, $i, j = 0, 1, 2, 3$ are the values of the second and third order derivatives for the functions $f(x, y)$ and $g(x, y)$.

Define the space of continuous real-valued functions as $C = C([-\tau_0, 0], \mathbb{R}^4)$.

In $\tau = \tau_0 + \mu, \mu \in \mathbb{R}$, we regard μ as the bifurcation parameter. For $\Phi \in C$ we define a linear operator:

$$L(\mu)\Phi = A\Phi(0) + B\Phi(-\tau)$$

where A and B are given by (11) and a nonlinear operator $F(\mu, \Phi) = F(\Phi(0), \Phi(-\tau))$, where $F(\Phi(0), \Phi(-\tau))$ is given by (19). According to the Riesz representation theorem, there is a matrix whose components are bounded variation functions, $\eta(\theta, \mu)$ with $\theta \in [-\tau_0, 0]$ so that:

$$L(\mu)\Phi = \int_{-\tau_0}^{0} d\eta(\theta, \mu)\phi(\theta), \quad \theta \in [-\tau_0, 0].$$

For $\Phi \in C^1([-\tau_0, 0], \mathbb{R}^4)$ we define:

$$\mathcal{A}(\mu)\Phi(\theta) = \begin{cases} \dfrac{d\Phi(\theta)}{d\theta}, & \theta \in [-\tau_0, 0) \\ \int\limits_{-\tau_0}^{0} d\eta(t,\mu)\phi(t), & \theta = 0, \end{cases}$$

$$R(\mu)\Phi(\theta) = \begin{cases} 0, & \theta \in [-\tau_0, 0) \\ F(\mu, \Phi), & \theta = 0. \end{cases}$$

We can rewrite (18) in the following vector form:

$$\dot{u}_t = \mathcal{A}(\mu)u_t + R(\mu)u_t \tag{20}$$

where $u = (u_1, u_2)^T$, $u_t = u(t+\theta)$ for $\theta \in [-\tau_0, 0]$.

For $\Psi \in C^1([0, \tau_0], \mathbb{R}^{*4})$, we define the adjunct operator $\mathcal{A}^*$ of $\mathcal{A}$ by:

$$\mathcal{A}^*\Psi(s) = \begin{cases} -\dfrac{d\Psi(s)}{ds}, & s \in (0, \tau_0] \\ \int\limits_{-\tau_0}^{0} d\eta^T(t,0)\psi(-t), & s = 0. \end{cases}$$

We define the following bilinear form:

$$< \Psi(\theta), \Phi(\theta) >= \bar{\Psi}^T(0)\Phi(0) - \int_{-\tau_0}^{0}\int_{\xi=0}^{\theta} \bar{\Psi}^T(\xi - \theta)d\eta(\theta)\phi(\xi)d\xi,$$

where $\eta(\theta) = \eta(\theta, 0)$.

We assume that $\pm i\omega_0$ are eigenvalues of $\mathcal{A}(0)$. Thus, they are also eigenvalues of $\mathcal{A}^*$. We can easily obtain:

$$\Phi(\theta) = ve^{\lambda_1\theta}, \quad \theta \in [-\tau_0, 0] \tag{21}$$

where $v = (v_1, v_2)^T$,

$$v_1 = -a\rho_{01}, v_2 = \lambda_1 + b + a\rho_{10},$$

is the eigenvector of $\mathcal{A}(0)$ corresponding to $\lambda_1 = i\omega_0$ and

$$\Psi(s) = we^{\lambda_2 s}, \quad s \in [0, \infty)$$

where $w = (w_1, w_2)$,

$$w_1 = \frac{w_2 c\gamma_{10} e^{-\lambda_1 \tau}}{b + \lambda_1 + a\rho_{10}}, w_2 = \frac{1}{\bar{\eta}},$$

$$\eta = v_1 \frac{c\gamma_{10} e^{-\lambda_2 \tau}}{b + \lambda_2 + a\rho_{10}} + v_2 - \frac{c\gamma_{10} v_1 + c\gamma_{01} v_2}{\lambda_1^2}(-\tau_0 \lambda_1 e^{-\lambda_1 \tau_0} - 1 + e^{-\lambda_1 \tau_0})]$$

is the eigenvector of $\mathcal{A}(0)$ corresponding to $\lambda_2 = -i\omega_0$.

We can verify that: $< \Psi(s), \Phi(s) >= 1, < \Psi(s), \bar{\Phi}(s) >=< \bar{\Psi}(s), \Phi(s) >= 0, < \bar{\Psi}(s), \bar{\Phi}(s) >= 1$.

Using the approach of Hassard [5], we next compute the coordinates to describe the center manifold Ω_0 at $\mu = 0$. Let $u_t = u_t(t + \theta), \theta \in [-\tau_0, 0)$ be the solution of equation (20) when $\mu = 0$ and

$$z(t) =< \Psi, u_t >, \quad w(t, \theta) = u_t(\theta) - 2Re\{z(t)\Phi(\theta)\}.$$

On the center manifold Ω_0, we have:

$$w(t, \theta) = w(z(t), \bar{z}(t), \theta)$$

where

$$w(z, \bar{z}, \theta) = w_{20}(\theta)\frac{z^2}{2} + w_{11}(\theta)z\bar{z} + w_{02}(\theta)\frac{\bar{z}^2}{2} + w_{30}(\theta)\frac{z^3}{6} + \ldots$$

in which z and $\bar{z}$ are local coordinates for the center manifold Ω_0 in the direction of Ψ and $\bar{\Psi}$ and $w_{02}(\theta) = \bar{w}_{20}(\theta)$. Note that w and u_t are real.

For solution $u_t \in \Omega_0$ of equation (20), as long as $\mu = 0$, we have:

$$\dot{z}(t) = \lambda_1 z(t) + g(z, \bar{z}) \tag{22}$$

where

$$\begin{aligned} g(z, \bar{z}) &= \bar{\Psi}(0)F(w(z(t), \bar{z}(t), 0) + 2Re(z(t)\Phi(0))) = \\ &= g_{20}\frac{z(t)^2}{2} + g_{11}z(t)\bar{z}(t) + g_{02}\frac{\bar{z}(t)^2}{2} + g_{21}\frac{z(t)^2\bar{z}(t)}{2} + \ldots \end{aligned}$$

where

$$g_{20} = F_{20}^1 \bar{w}_1 + F_{20}^2 \bar{w}_2, g_{11} = F_{11}^1 \bar{w}_1 + F_{11}^2 \bar{w}_2, g_{02} = F_{02}^1 \bar{w}_1 + F_{02}^2 \bar{w}_2, \tag{23}$$

with

$$\begin{aligned}
F_{20}^1 &= -a(\rho_{20}v_1^2 + 2\rho_{11}v_1v_2 + \rho_{02}v_2^2,\\
F_{20}^2 &= c[\gamma_{20}v_1^2e^{-2\lambda_1\tau} + \gamma_{02}v_2^2e^{-2\lambda_1\tau} + 2\gamma_{11}v_1v_2e^{-2\lambda_1\tau}],\\
F_{11}^1 &= -a[\rho_{20}v_1\bar{v}_1 + \rho_{11}(v_1\bar{v}_2 + \bar{v}_1v_2) + \rho_{02}v_2\bar{v}_2],\\
F_{11}^2 &= c[\gamma_{20}v_1\bar{v}_1 + \gamma_{11}(v_1\bar{v}_2 + \bar{v}_1v_2) + \gamma_{02}v_2\bar{v}_2],\\
F_{02}^1 &= \bar{F}_{20}^1, F_{02}^2 = \bar{F}_{20}^2,
\end{aligned}$$

and

$$g_{21} = F_{21}^1\bar{w}_1 + F_{21}^2\bar{w}_2 \tag{24}$$

where

$$\begin{aligned}
&F_{21}^1 = -a[\rho_{20}(2v_1w_{11}^1(0) + \bar{v}_1w_{20}^1(0)) + 2\rho_{11}(v_1w_{11}^2(0)+\\
&\frac{\bar{v}_1w_{20}^2(0)}{2} + \frac{\bar{v}_2w_{20}^1(0)}{2} + v_2w_{11}^1(0)) + \rho_{02}(2v_2w_{11}^2(0) + \bar{v}_2w_{20}^2(0))-\\
&\rho_{30}v_1^2\bar{v}_1 + 2\rho_{21}v_1v_2\bar{v}_1 + 2\rho_{12}v_1v_2\bar{v}_2 + \rho_{03}v_2^2\bar{v}_2 + \rho_{21}v_1^2\bar{v}_2 + \rho_{12}\bar{v}_1v_2^2]
\end{aligned}$$

$$\begin{aligned}
&F_{21}^2 = c[\gamma_{20}(2v_1w_{11}^1(-\tau)e^{-\lambda_1\tau} + \bar{v}_1w_{20}^1(-\tau)e^{\lambda_1\tau}) + 2\gamma_{11}(v_1w_{11}^2(-\tau)e^{-\lambda_1\tau}+\\
&+\frac{\bar{v}_1w_{20}^2(-\tau)e^{\lambda_1\tau}}{2} + \frac{\bar{v}_2w_{20}^1(-\tau)e^{\lambda_1\tau}}{2} + v_2w_{11}^1(-\tau)e^{-\lambda_1\tau}) + \gamma_{02}(2v_2w_{11}^2(-\tau)e^{-\lambda_1\tau}+\\
&+\bar{v}_2w_{20}^2(-\tau)e^{\lambda_1\tau}) + \gamma_{30}v_1^2\bar{v}_1e^{-\lambda_1\tau} + \gamma_{21}(2v_1\bar{v}_1v_2e^{-\lambda_1\tau} + v_1^2\bar{v}_2e^{-\lambda_1\tau})+\\
&+\gamma_{12}(2v_1v_2\bar{v}_2e^{-\lambda_1\tau} + \bar{v}_1v_2^2e^{-\lambda_1\tau}) + \gamma_{03}v_2^2\bar{v}_2e^{-\lambda_1\tau}].
\end{aligned}$$

The vectors $w_{20}(\theta)$, $w_{11}(\theta)$ with $\theta \in [-\tau, 0]$ are given by:

$$\begin{aligned}
w_{20}(\theta) &= -\frac{g_{20}}{\lambda_1}ve^{\lambda_1\theta} - \frac{\bar{g}_{02}}{3\lambda_1}\bar{v}e^{\lambda_2\theta} + E_1e^{2\lambda_1\theta}\\
w_{11}(\theta) &= \frac{g_{11}}{\lambda_1}ve^{\lambda_1\theta} - \frac{\bar{g}_{11}}{\lambda_1}\bar{v}e^{\lambda_2\theta} + E_2
\end{aligned} \tag{25}$$

where

$$E_1 = -(A + e^{-2\lambda_1\tau_0}B - 2\lambda_1 I)^{-1}F_{20}, \quad E_2 = -(A+B)^{-1}F_{11},$$

where $F_{20} = (F_{20}^1, F_{20}^2)^T$, $F_{11} = (F_{11}^1, F_{11}^2)^T$.

Based on the above analysis and calculation, we can see that each g_{ij} in (23), (24) are determined by the parameters and delay of system (2). Thus, we can explicitly compute the following quantities:

$$\begin{aligned}
&C_1(0) = \frac{i}{2\omega_0}(g_{20}g_{11} - 2|g_{11}|^2 - \frac{1}{3}|g_{02}|^2) + \frac{g_{21}}{2},\\
&\mu_2 = -\frac{Re(C_1(0))}{M}, T_2 = -\frac{Im(C_1(0)) + \mu_2 N}{\omega_0}, \beta_2 = 2Re(C_1(0)),
\end{aligned} \tag{26}$$

where M and N are given by (16) and (17).

In short, this leads to the following result:

Theorem 3. *In formulas (26), μ_2 determines the direction of the Hopf bifurcation: if $\mu_2 > 0(< 0)$, then the Hopf bifurcation is supercritical (subcritical) and the bifurcating periodic solutions exist for $\tau > \tau_0(< \tau_0)$; β_2 determines the stability of the bifurcating periodic solutions: the solutions are orbitally stable (unstable) if $\beta_2 < 0(> 0)$; and T_2 determines the period of the bifurcating periodic solutions: the period increases (decreases) if $T_2 > 0(< 0)$.*

4. Numerical example.

In this section we find the waveform plots through the formula:

$$X(t+\theta) = z(t)\Phi(\theta) + \bar{z}(t)\bar{\Phi}(\theta) + \frac{1}{2}w_{20}(\theta)z^2(t) + w_{11}(\theta)z(t)\bar{z}(t) + \frac{1}{2}w_{02}(\theta)\bar{z}(t)^2 + X_0,$$

where $z(t)$ is the solution of (20), $\Phi(\theta)$ is given by (21), $w_{20}(\theta), w_{11}(\theta), w_{02}(\theta) = \bar{w}_{20}(\theta)$ are given by (25) and $X_0 = (y_{10}, y_{20})^T$ is the equilibrium state.

For the numerical simulations we use Maple 9.5. and the data from [10]: the degradation of p53 through ubiquintin pathway $a = 3 \times 10^{-2}\text{sec}^-1$, the spontaneous degradation of P53 is $b = 10^{-4}\text{sec}^{-1}$, the dissociation constant between P53 and Mdm2 gene is $k_1 = 28$, the degradation rate of Mdm2 protein is $d = 10^{-2}\text{sec}^{-1}$, the P53 protein production rate is $S = 0.01\text{sec}^{-1}$ and the production rate of Mdm2 is $c = 1\text{sec}^{-1}$. For this date we consider the different values for the constant k. By changing instantaneously the dissociation constant k the response of the system is different.

For $k = 17.5$ we obtain: the equilibrium point $y_{10} = 1.674122637$, $y_{20} = 4.587857801$, the coefficients which describe the limit cycle: $\mu_2 = 0.002340098338$, $\beta_2 = -0.000001452701020$, $T_2 = 0.00007793850775$ and $\omega_0 = 0.04577286901$, $\tau_0 = 60.52296388$. Then the Hopf bifurcation is supercritical, the solutions are orbitally stable and the period of the solution is increasing. The wave plots are displayed in fig1 and fig2:

Fig.1. $(t, y_1(t))$

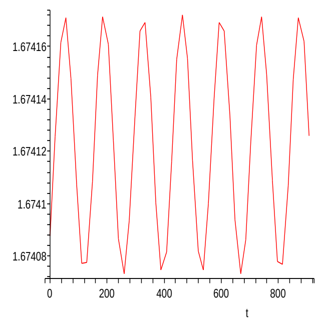
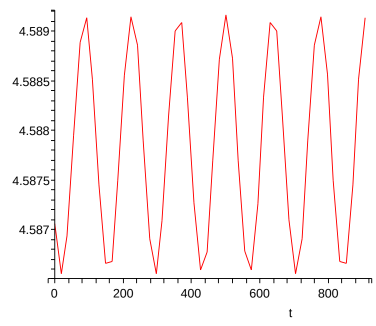


Fig.2. $(t, y_2(t))$



For $k = 120$ we obtain: the equilibrium point $y_{10} = 3.853801769$, $y_{20} = 11.20502079$, the coefficients which describe the limit cycle: $\mu_2 = -8.219839362 \cdot 10^{-7}$, $\beta_2 = 2.0434666644 \cdot 10^{-10}$, $T_2 = 2.243699328 \cdot 10^{-7}$ and $\omega_0 = 0.02923152517$, $\tau_0 = 92.68683554$. Then the Hopf bifurcation is subcritical, the solutions are orbitally unstable and the period of the solution is increasing. The wave plots are presented in fig3 and fig4:

Fig.3. $(t, y_1(t))$

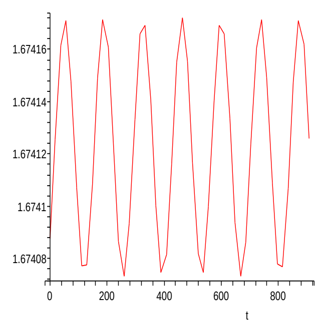
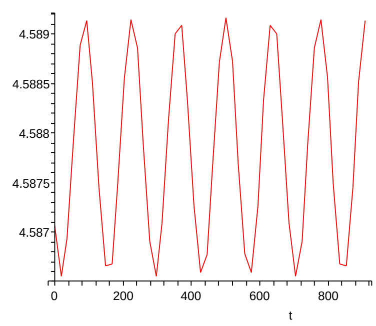
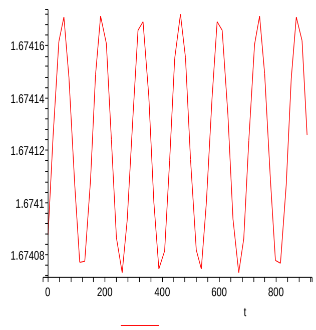
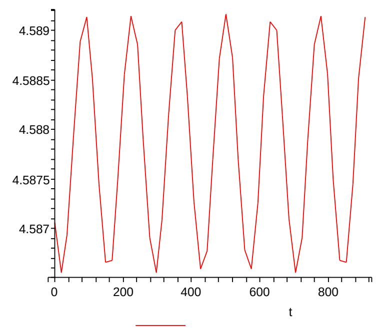


Fig.4. $(t, y_2(t))$



For $k = 1750$ we obtain: the equilibrium point $y_{10} = 14.88816840$, $y_{20} = 34.27918463$, the coefficients which describe the limit cycle: $\mu_2 = 1.104273140 \cdot 10^{-11}$, $\beta_2 = -6.4139104 \cdot 10^{-16}$, $T_2 = 1.924908056 \cdot 10^{-11}$ and

$\omega_0 = 0.01423761906$, $\tau_0 = 174.4149631$. Then the Hopf bifurcation is supercritical, the solutions are orbitally stable and the period of the solution is increasing. The wave plots are given in fig5 and fig6:

Fig.5. $(t, y_1(t))$	Fig.6. $(t, y_2(t))$
	

5. Conclusions.

For the present model, we obtain an oscillatory behavior similar with the findings in [10], according with the qualitative study.

We have proved that a limit cycle exists and it is characterized by the coefficients from (26). For different values for the equilibrium constant k, in Section 4 we obtain stable or unstable periodic solutions with increasing periods, via a Hopf bifurcation.

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